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Pharmacotherapy, steroid injection, fat graft, PIP external fixators and other techniques

Maarten van Nuffel[1]
Ilse Degreef[2]
[1]Orthopedic Department, University Hospitals Leuven, Leuven, Belgium
[2]Leuven University Hospitals, Leuven, Belgium

Introduction

Dupuytren's disease (DD) is a disease in every sense of the word. This means that a cure is not likely to be achieved with surgery alone. The origin of the nodules and contractures is unknown. Some patient have clinical features of a diathesis with more severe expression of fibrosis [1]. The more severe forms of DD usually present with extensive involvement of both hands in several finger rays and with higher recurrence rates after surgical correction of the contractures. The surgical technique does not predict recurrence and the removal of all affected fibrotic tissue, does not guarantee indefinite 'healing' of DD [2].

In this chapter, we highlight the non-operative treatment methods, except those addressed in other chapters (radiotherapy, splinting, minimal invasive techniques such as needle fasciotomy, collagenase injections or segmental fasciotomy. Here, we highlight current and future options of disease control with pharmacotherapy. The adjuvant techniques of fat grafting and external fixators are also treated in this chapter.

Pharmacotherapy

Why pharmacotherapy?

In the biology of DD, as discussed in an earlier chapter, the key is the activation of the fibroblast. If 'activated', it then turns into a myofibroblast phenotype with contractile properties and the ability to produce collagen [3]. By a creeping substitution process, the contractures seen in Dupuytren's Disease are static and can become severely disabling for the hand function. It is unclear if the myofibroblast is de-activated or disappears by apoptosis once contractures are established and appear stable.

The pathways of activation and possible de-activation (or apoptosis) of the (myo-)fibroblasts are the subject of numerous ongoing laboratory studies [4]. Both *in vivo* and *in vitro* research lead to a continuously increasing knowledge of growth factors and their receptors that may steer the cell cycle, migration, proliferation, (in-)activation and apoptosis. Evidently, the addition of certain products to influence these processes, may lead towards future pharmacotherapy, in which medication (systemic, topical lotions or injection) may one day become available to improve surgical outcome, prevent recurrence or even reverse contractures in DD.

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How can pharmacotherapy be delivered?

Drugs can be administered topically, by injection or implantation or systemically (peroral/intravenous/intramuscular administration). The easiest applicable method is preferable since the patient will be more compliant if administration is easy and user friendly. The most local and non-invasive manner of drug administration is preferred. By avoiding systemic administration, side effects will usually be more limited. Finally, if surgery (for instance the implantation of a drug carrier) can be avoided, the induction of scar tissue formation and thus new fibrotic processes can be avoided (as well as the burden of surgery to the patient). Collagenase injections, as discussed in the next chapter, act as an enzymatic fasciotomy, with little disease modification but rather symptomatic treatment of the established contractures. Disease modifying injection therapy as corticosteroids may be an option in future disease control.

What do we know? A literature review

What is currently known on pharmacotherapy in DD? A thorough literature review reveals sparse research evidence. Numerous pharmacotherapeutic options are suggested and most of these can be categorized as anti-inflammatory drugs (assuming DD to be a chronic inflammatory process), anti-mitotic treatment options (DD as a neoplasm) and other pharmacological targets such as hormonal therapy. The available reported research on pharmacotherapy in DD is reviewed below.

Steroids

Oral steroids

Baxter and colleagues were the first to report on cortisone in DD in 1946 [5]. Based on the beneficial effects in rheumatoid arthritis, they injected the nodules in 5 patients, but saw no improvement. Both intramuscular and oral administration of cortisone in 3 patients was unsuccessful either clinically or histologically after surgical removal. Lastly, they administered cortisone combined with surgery in 4 patients and found no side effects and good clinical outcome, which they attributed to the cortisone administration.

In 1951 Tilley and McDonald first reported on the postoperative administration of corticoids after surgery for DD in a study of 19 patients, of whom 7 patients received 200–400 mg oral cortisone after fasciectomy pre- and/or postoperatively in varying time-intervals [6]. The excised palmar fascia was histologically examined and no differences were found. Although a control group was used, the study had too many variables and was far from level I, but since the authors did not find a difference, they advocated not using cortisone and even stopping examining the option in DD.

In 1954, Bernstein and colleagues reported on postoperative **cortisone** treatment in DD in 14 cases [7]. Back then, total fasciectomy was popular, but recurrences were still seen and remained worrisome. Cortisone was thus introduced in the realm of therapy around 2 years earlier to retard the development of connective tissue and inhibit the formation of granulation tissue. Repeated parental and intralesional infiltrations, next to oral medication (100–200 mg cortisone daily) were administered. Postoperative systemic cortisone was administered from day 7 for 3 weeks after surgery. Results were promising; mobility seemed facilitated without wound healing problems even a year after cessation. Bernstein mentioned ‘remission’ state if the patient remained without symptoms of contracture. Back then, fibrosis diathesis was unknown and evidently, no differentiation amongst patients was made. An inflammatory background of DD was suspected and it was compared with rheumatism.

In 1999, Meek et al reported on a possible mechanism for steroid disease control in DD as a chronic inflammatory process [8]. They focused on the critical role of TGF-beta in fibrosis and the

transendothelial migration of inflammatory cell populations and advocate further research for clinical use of immunomodulation of DD, since they are strongly convinced that steroids may offer a therapeutic intervention to prevent recommencement of the inflammatory process and subsequent fibrosis after surgery for DD.

Steroid injections

Based on the experience of steroid injections in hypertrophic scars and keloids, injecting the nodules in DD and Ledderhose's Disease with corticosteroids such as **Triamcinolone** was proposed. This can be used both as a separate procedure and as an adjuvant therapy in percutaneous needle aponeurotomy. Triamcinolone degrades the insoluble collagen in hypertrophic scars and keloids to salt-soluble collagen, which is absorbed by the body and excreted [9]. In 1985, Pentland and Anderson reported on a successful case treatment with 5 consecutive monthly intralesional injections with steroids (40 mg/ml) in recurrent plantar fibrosis [10].

Trojian and colleagues suggested the use of Triamcinolone acetonide injection in isolated nodules without finger contracture to prevent progression, cord development and finger contracture [11]. However, hard evidence for this is still lacking. This suggestion was based on the work of Ketchum and Donahue, who reported on 63 patients with only mild nodular forms (no contractures), treated with intralesional steroid injections with a 97% success rate [12]. Nodules softened or flattened and this was considered disease regression. In 50%, nodules recurred 1 to 3 years later and treatment was repeated if needed. However, they did not see any success in contracture treatment and since only Tubiana stage 1 patients were included, fibrosis diathesis was likely to be low in the investigated population. Al-Qattan commented that since triamcinolone is known to decrease the alfa2-macroglobulin, a potent inhibitor of collagenase, it actually increases the intrinsic collagenase activity in DD. He therefore suggested comparing collagenase injections with steroid injections [13].

Three years after their report on the possible role of steroids in Dupuytren's treatment, Meek and colleagues studied the role of programmed cell death in steroid treatment. They found that steroids reduced specific Dupuytren's fibroblast proliferation with increasing rates of apoptosis of both fibroblasts and inflammatory cells but not of palmar fascia and fascia lata cells [14].

In 2012, McMillan and Binhammer presented a randomized controlled trial on steroid injection during needle fasciotomy in 47 patients [15]. Although the amount of triamcinolone acetonide did not correlate with the mobility improvement, it appeared to increase significantly the 6-month follow-up clinical result compared to placebo injections.

However, due to reported complications of dermal atrophy, skin depigmentation and sporadically reported tendon rupture, the routine use of these injections is not recommended [16]. These findings are similar to the ones in La Peyronie's Disease [17], [18].

Topical steroids

Shelley and Shelley reported briefly in 1993 on the successful outcome of topical treatment of Dupuytren's Disease in 6 patients, mostly in nodular regression [19]. In the Lancet, Freeman responded to Shelley that topical 0.05% **clobetasol propionate** cream twice daily and 0.05% **tretinoin** cream once daily in Dupuytren's Disease himself without success [20]. Therefore, the only reports are levels of eminence based evidence and case series.

Interferon

In 1994, Pittet and colleagues investigated the effect of **gamma-interferon**, a cytokine produced by T-helper lymphocytes, known to decrease fibroblast replication, activation and collagen production [21]. Based on experience with scar tissue management, they injected the interferon in 14 Dupuytren's patients within nodules and sizes decreased, as did their symptoms. Sanders et al. demonstrated decreased myofibroblast contractility in Dupuytren's fibroblasts, as in control tissue in collagen lattice models [22]. Tomasek and colleagues suggested that interferon gamma may potentially be used in nonsurgical therapy DD [3]. Similar effects have been found in La Peyronie's Disease: interferon injection in plaques can inhibit fibroblast proliferation, decrease extracellular matrix production and increase the production of collagenase [23]. This leads to clinical improvement of the penile curvature and decrease of the plaque size [24].

Colchicine

The effects of **colchicine** were first studied by Dominguez-Malagon et al. in 1992, were the drug was administered in 3 patients, 1 with Dupuytren's Disease [25]. Tumor size was reduced and contracture improved. Ultrastructural changes indicated desactivation of myofibroblasts and reduced collagen in the affected tissues. Colchicine is known to induce collagenase activity and to decrease collagen synthesis. Akkus et al. attempted oral administration of colchicine for 3 to 5 months in 24 patients with Peyronie's Disease in 1994 and in this very similar fibrosis affection, some promising results with improving penile curvatures. However, the concomitant Dupuytren's contractures in these patients, did not improve [26].

Cytostatic drugs

Jemec and colleagues in 2000 studied the *in vitro* effects of **5-FU** on Dupuytren's myofibroblasts [27]. 5-FU is a cytostatic drug known to inhibit thymidylate synthase, which inhibits thymidine synthesis, needed for DNA synthesis. They demonstrated an inhibitory effect on proliferation and differentiation of myofibroblast cell cultures, harvested from Dupuytren's tissue. They based their idea on the use of 5-FU in scar tissue management of the eye in glaucoma surgery and advocate further research on the possible usefulness of this agent in DD. Bulstrode initiated a RCT in 15 patients with intra-operative 5 minutes topical 5FU versus placebo application and although no complications were encountered, the beneficial effect was not significant [28].

Kraljevic and colleagues reported the anti-proliferative drug effects in patients operated on for Dupuytren's contractures. They found a short-term beneficial effect of an **N-sulfonylpyridimide** derivative, lost after 6 and 14-day treatments. Amidino-substituded bezimidazo quinolone also appeared to exert a non-specific anti-proliferative activity [29].

Verjee and colleagues reported on **TNF** (tumor necrosis factor, a cytokine implicated in tumor regression) as a possible therapeutic target to down-regulate myofibroblast differentiation and activity in early DD. Based on their experimental findings on cultured myofibroblasts of Dupuytren's nodules, they suggest that local injection of anti-TNF may prevent progression to contractures [30].

Reproductive hormones

Since they demonstrated that androgen receptors are expressed in the myofibroblasts of Dupuytren's nodules, Pagnotta investigated the effect of 5 alfa-dihydrotestostereone on cultured cells in 2003 [31].

Tamoxifen is a synthetic non-steroidal anti-estrogen known to modulate the production of TGF beta. It is primarily used in breast cancer in female patients, but it has also been applied in males with breast cancer, gynaecomastia, prostate cancer, and acromegaly [32]. Generally it is well tolerated, but side effects include gastrointestinal distress and alopecia [33]. In these pathologies, treatment strategies include low-dose tamoxifen (30 mg orally per day) and high-dose tamoxifen (60–120 mg orally per day).

Furthermore, it has been used in the treatment of aggressive fibrotic diseases, for example, idiopathic retroperitoneal fibrosis, and recurrent desmoid tumors [34], [35], [36], [37],[38]. They found an increased fibroblast activation and proliferation with secondary down regulation of the androgen receptors. Kuhn et al suggested with their in vitro work on Dupuytren's myofibroblast contractility, that tamoxifen might be of value in the treatment of DD as they demonstrated a decrease in TGF expression and in contraction rate in fibroblast cultures on collagen lattices, harvested from Dupuytren's affected fascia and carpal tunnel affected fascia as a control [39]. In response to the suggestions of Kuhn, a level I clinical trial in high fibrosis diathesis patients with DD was undertaken. Tamoxifen appeared to improve short-term outcome of segmental fasciectomy[40]. However, the beneficiary effect was lost within 2 years and the side effects of this drug may not allow for longer therapy endurance or investigation [41].

In the treatment of hypertrophic scars, the topical application of Tamoxifen has been proposed [42]. Toremifene, a chlorinated Tamoxifen analog, was administered by means of methylcellulose in an animal model for melanoma [43]. Theoretically, side effects of these products will be less in topical treatment, since the plasma concentration will never be as high in systemic therapy [44]. However, there are currently no published data about its use in DD.

Verapamil

There are anecdotal reports of the local use of **Verapamil 15% gel** to the nodules. Verapamil is a calcium channel blocker and fibroblasts need calcium to produce collagen. Theoretically, this medication could decrease the collagen production and increase the collagenase activity. There is no hard evidence on this treatment method [45].

In Peyronie's Disease, **verapamil injections** into the plaques are widely used with a standard injection dose of 10 mg given every 2 weeks for 12–24 weeks, which is safe and well tolerated [46], [47], [48], [49]. Nicardipine is another calcium channel blocker that has shown good results in La Peyronie's Disease [50]. However, other studies have shown that calcium channel blocking injections may have a less beneficial outcome [51], [52].

Benzodiazepines

Opinion on the coexistence of DD and epilepsy differs. Many authors suggest that **phenobarbital**, a common anti-epileptic drug, may have a role in both genesis and development of DD. Prolonged administration of Phenobarbital may have an associated risk of developing DD, presumably mediated through the peripheral stimulation of tissue growth factor [53]. Tripoli and colleagues suggested a dose-dependent evolution after surgery in 3 patients, which improved after **carbamazepine** substitution [54].

Other suggestions – miscellaneous

With the identification of basic fibroblast growth factor in Dupuytren's tissue, Lappi et al. suggested in 1992 that **saporin** as a ribosome-inactivating protein may be cytotoxic to cells with the FGF receptor as in Dupuytren's myofibroblasts, but no clinical trial has been reported [55].

In 1996, Rayan and Tomasek investigated different pharmacological agents on Dupuytren's myofibroblasts *in vitro* as collagen lattice contraction essays [4]. They found possible promoting effects of **lysophosphatic acid** and in a lesser amount also of **angiotensin II, serotonin and prostaglandin F2 alpha**. In contrast, the in daily practice commonly used calcium blockers **nifedipine** and **verapamil**, and also **prostaglandins E1 and E2** seem to inhibit contraction. Knobloch hypothesized in 2009 that **N-acetyl-L-cystein** and ACE inhibitors may be helpful in reducing recurrence in DD, but no clinical trial was reported [56].

Bains formulated the hypothesis that based on the knowledge of fibroblast proliferation in wound healing and vascular surgery (arterial grafting), with the resemblance of myofibroblasts of smooth muscle

phenotypes, treatment with **VEGF** as a protein or via gene therapy, may be of value in DD management [57].

Recently, Kang and colleagues added **relaxin** to the possible targets. The relaxin gene responsible for the production of the naturally occurring hormone relaxin with its antifibrogenic effect, regarded as the pregnancy hormone facilitating gestation, childbirth and lactation and related to the insulin family of peptides, has been investigated in the laboratory possible target in DD [58].

Numerous topicals are used in the treatment of DD, but hardly any trials are reported. Emelife and colleagues [59] recently reported on a topical vasodilator, **nitroglycerin** in 2 cases, after surgery to prevent recurrent scar formation. **Vitamin E** has been suggested anecdotally to have beneficial effects on Dupuytren's contractures based on theoretical free radical oxygen scavenging effects as well as capacity for immune system modulation, but no significant clinical evidence has been reported. However, highly dosed intra-oral vitamin E may carry a significant side-effect risk [60]. In Peyronie's Disease, it is widely used because of low cost and absence of significant side effects. It can provide some pain relief in the acute phase of Peyronie's Disease and alleviate psychologic distress caused by this condition [61], [62].

Fat grafting

In the quest for other, minimal invasive techniques in the treatment of DD, Hovius and colleagues proposed a method of injecting an autologous lipoaspirate after percutaneous aponeurectomy [63]. They suggested this as an alternative to collagenase injections to avoid the disadvantages of an extensive inflammatory reaction and the risk of tendon damage. Given the positive effect of fat grafting in softening scars in other clinical conditions, the addition of fat grafting is supposed to decrease the recurrence rate. Prior to the aponeurotomy, fat is harvested from the abdomen or thigh using manual liposuction. The aponeurectomy itself is performed by a large number of small puncture wounds, working progressively from proximal to distal, in a wide area around the cord, thus releasing the skin completely from the underlying cord while gently extending the finger. This creates a space where the lipograft can be injected. Postoperatively, an extension splint is used at night for up to 20 weeks. The whole procedure takes about the same amount of time as an aponeurectomy (1 to 1.5 hours). During follow-up, the clinical aspect of the operated skin was more or less the same as normal skin, including the normal soft subcutaneous fat tissue. This is in contrast with most other procedures including fasciectomy. Reported complications are similar to other procedures, namely digital nerve injury, infection and complex regional pain syndrome. However, these seem to occur mostly in hands that have been previously operated apon. Recovery time was remarkably short, with most of the patients regaining use of the hand approximately 1 week after surgery. This procedure yields about a 30–40° increase in extension in both the proximal interphalangeal and the metacarpophalangeal joint at a follow-up of more than 40 weeks, has very high patient satisfaction; previously operated patients apparently prefer this to a fasciectomy. The possible mechanism behind this technique is the re-establishing of subcutaneous fat tissue in the hand, thus creating an interposition between the skin and the palmar fascia. Furthermore, the properties of the abdominal fat, which are different from the subcutaneous tissue in the hand, and the presence of stem cells with regenerative potential, may decrease the risk of recurrence. Fat grafting has already proven its beneficial effects in other clinical conditions, for example in radiotherapy and around chronic ulceration based on these principles [64], [65]. *In vitro* research has demonstrated that adipose-derived stem cells inhibit the contractile myofibroblast in DD. These stem cells seem to reduce the contraction of myofibroblasts in Dupuytren's nodules, decrease the expression of alpha-smooth muscle actin and even inhibit the proliferation of myofibroblasts. Stem cells derived from bone marrow do not seem to have the same properties [66]. Similar results have been obtained in Peyronie's Disease [67].

PIP external fixator

The proximal interphalangeal (PIP) joint remains one of the main causes of unsatisfactory results in the treatment of DD [68]. Extension splinting may improve the correction obtained in operative release [69]. During elongation of the palmar fascia, the tissue is reorganized. Microscopically, the collagen fibrils become more aligned in fibres parallel to the stretching force. Fibroblasts and myofibroblasts with a high biosynthetic activity and oxytalan-like microfibrils become aligned along these collagen fibres. This is a clear different organization compared to the usual cords and nodules in DD [70]. The underlying mechanism is believed to be an increased turnover of collagen, with changes in the cross-link profile. An increased amount of degradative enzymes: metalloproteinases, collagenase, gelatinase and cathepsins B and L, was demonstrated in tissue after soft tissue distraction and probably caused by tension on the fibroblasts [71].

Additional distraction can be applied with an external fixator, as shown by Messina and Messina [72], [73]. The operative release of checkrein ligaments in very severe flexion contractures of the PIP joint may be augmented by this technique. Thus, the position of the finger can be improved before surgery, which in some severe cases can even avoid the need for amputation [73]. Similar methods have been used in PIP joint contractures due to other reasons [74], [75]. By directly transmitting the external force as a torque to the bone, the pressure problems usually associated with splinting or casting can be avoided.

Several different constructs and devices have been proposed. The Digit Widget™ (Hand Biomechanics Lab Inc, Sacramento, CA) is one example of these devices that use dynamic external bone fixation to correct the soft tissue flexion contracture. Initially, these devices were used to provide soft tissue distraction prior to fasciectomy, to improve the outcome regarding the PIP joint range of motion. However, it seems that sometimes the external distraction alone can yield enough improvement without the need for further operative treatment [76], [77], [78].

Different companies produce similar soft tissue distractors to correct PIP joint contracture in Dupuytren's Disease. For example, the Pipster [79], Multiplanar Distractor [74], [80], [81]. All use the same principles and yield comparable results. However, when used to provide postoperative traction, external fixators usually yield poor results and early recurrence [80], [82].

Citron and Messina compared two different external traction devices prior to fasciectomy: the "Tecnica di Estension Continua" (TEC), a rather large device that can extend multiple digits at the same time and the Verona device, a smaller device, used on a single digit. They found an improvement in total active range of motion in the PIP joint from a mean of 80° to 29° at 18 months follow-up. However, no significant difference between the two devices could be detected and Complex Regional Pain Syndrome (CRPS) occurred in no less than 5 of the 13 treated patients. They stated that the use of these external fixators should be only one component of a carefully planned programme in suitable cooperative patients. The high incidence of CRPS in this series was probably caused by a too rapid extension of the fingers, according to the authors [82]. In the original description, Messina insisted that the traction at 2 mm per day be subdivided into four increments of 0.5 mm to allow physiological softening of the contracted bands [73].

White and colleagues developed a very simple external fixator placed on the dorsal side of the finger which provided traction by means of elastic bands that were tensioned during hand therapy. Movement of the finger was still possible. After four weeks of traction, they performed a dermofasciectomy, with full-thickness skin grafting over the proximal phalanx. Virtually full correction was achieved prior to operation in most cases. The patients were followed for a mean of 20.6 (6–48) months. The mean preoperative PIPJ deformity improved from 75° to 37° postoperatively. Overall, 69% of results were rated as good to excellent. There was only one case of CRPS in this series of 38 fingers in 27 patients [83].

Other therapies

Shock wave therapy

There are few data on high-energy focused extracorporeal shockwave therapy. Knobloch and colleagues found pain reducing effects in 6 patients with plantar fibrosis, but research is needed to evaluate possible beneficial effects in DD [84], [85]. They hypothesized that this function and contractures in DD may also benefit from this non-invasive tool.

Extracorporeal shock wave therapy (ESWT) has been shown to cause damage to penile plaques in Peyronie's Disease, giving rise to an inflammatory reaction resulting in lysis of the plaque, increased vascularity and finally plaque resorption [86]. It has been shown to improve pain and quality of life scores, without significant effect on plaque size or penile curvature [87]. A combination therapy of ESWT with intralesional verapamil injections resulted in significant improvements in pain in 91.5% and plaque reduction in 49% [88].

Cryosurgery

In Ledderhose disease, a prospective analysis of cryotherapy by Allen and colleagues (percutaneous freezing of the plantar nodules) in 59 patients offered a significant decrease in pain [89]. This minimal invasive procedure was repeated twice or in some cases 3 times if needed, but no long term analysis is available thus far and no experience is reported in DD.

Conclusion

Long standing and more recent data on the basic science and the treatment options for DD, may lead to a patient-specific treatment plan depending on the severity of the affection and the underlying fibrosis diathesis. In pharmacotherapy, disease control is the primary goal. Efficacy, side effects and risk-benefit analysis are needed for every treatment proposal. Surgical or enzymatic fasciotomy may continue to be the first option in releasing contractures, but the prevention of recurrence motivates translational research into adequate pharmacotherapy and other non-surgical treatment options. A lack of evidence on treatment options contrasts with the growing knowledge on the underlying cellular pathways in DD. Perhaps one day contractures may become manageable without surgical intervention, excluding the hand surgeon as the primary caregiver for patients with DD [1].

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